## REMARKS

1. Restriction Requirement

Claims 1-41 are currently pending. The Examiner has indicated that the Restriction Requirement has been made Final and that Applicant's comments challenging the Restriction Requirement cannot be considered by the Examiner but must be directed to the Director of Technology Center 1600 in the form of a petition. Accordingly, claims 9-11, 14-19, 22, 27, 28 and 30-35 have been withdrawn from consideration.

2. Drawings

The Examiner has indicated that the corrected or substitute drawings received on March 10, 2003 were not acceptable because the conditions for accepting color photographs had not been met. Specifically, the Examiner alleges that a petition under 37 C.F.R. §1.84(a)(2) had not been submitted. Applicant has enclosed copies of papers filed on April 21, 2003 submitting three sets of the colored drawings and the required petition for the acceptance of color photographs. Although the Examiner now indicates that Figures 1 and 8 filed on April 28, 2003 were "falling off of the sheet", he has indicated that the Figures 1 and 8 filed on March 10, 2003 were acceptable. Accordingly, Applicant believes that all of the required drawing corrections have been satisfied. Applicant submits that the foregoing remarks and attached documents demonstrate that Applicant complied with the applicable rules governing the submission of colored photographs and respectfully requests reconsideration and removal of the objection.

3. Specification

The Examiner has objected to the Specification because the "Brief Description" for Figure 2a-2m fails to contain a reference to the SEQ ID NOs contained therein. The Examiner has also indicated that the sequence listing must be amended to include the amino acid sequences disclosed in Figure 2a-2m. Applicant would like to point out that a substitute Sequence Listing which includes the amino acid sequences disclosed in Figure 2a-2m was submitted on August

27, 2001 and the Specification was amended accordingly. (Please see enclosed.) Reconsideration and removal of the objection is respectfully requested.

4. Lack of Utility/Lack of Enablement

Claims 1-7, 20, 21 and 23-26 as well as claims 8, 12, 13, 29 and 36-41 stand rejected under 35 U.S.C. §101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Since the claims are not supported by either a specific and substantial asserted utility or a well-established utility, the Examiner has further rejected the claims under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner states that Applicant's prior arguments were considered but found unpersuasive. Applicant's arguments that the LOBO gene and the proteins encoded by the nucleotide sequence were involved in mitosis, cell cycle, etc. were found to be "postulations of biological activity" and not an unequivocal assertion of the function of the LOBO gene/protein. Similarly, Applicant's arguments regarding the role of the LOBO gene/protein to treat various bone growth developmental diseases was rejected as the Specification failed "to identify a hereditary disease that can either be diagnosed or treated using the claimed invention". Moreover with respect to the treatment of achondroplasia (AHO), the Examiner found that the Specification fails to support a finding that reducing expression of LOBO would ameliorate AHO. Finally, the Examiner rejected Applicant's arguments that the LOBO gene could be used for cartilage tissue engineering or producing cartilage or tissue substitutes as being mere attorney argument unsupported by any objective evidence or explanation as to how the skilled artisan would arrive at such a use. Applicant respectfully traverses.

The claims are directed to isolated nucleic acid molecules which encode a protein involved in bone growth and development, host cells transformed with these isolated nucleic acid molecules and diagnostic or pharmaceutical compositions comprising these nucleic acid molecules. To satisfy the utility requirement, an Applicant need only claim an invention that is directed to statutory subject matter and is "useful" for some purpose. The Examiner has already acknowledged that the claims are directed to statutory subject matter. However, the Examiner maintains that application fails to explicitly or implicitly describe a "useful" purpose for the invention. Applicant disagrees. Applicant submits that the application sets forth at least one

"specific and substantial utility" for the claimed invention. In particular, the application implicitly describes using the claimed isolated nucleic acid molecules to create non-human transgenic animals. Creating such transgenic animals is clearly a "real world" use that satisfies the statutory requirements. Accordingly, applicant submits that at least claims 1-8, 29 and 36-41 satisfy the utility requirement and thus the enablement requirement under 35 U.S.C. §112, first paragraph.

Applicant submits that claims 12-13 and 23-26 which are directed to diagnostic or pharmaceutical compositions comprising the nucleic acid molecules also satisfy the utility and enablement requirements. The Examiner argues that the disclosure fails to identify a specific hereditary disease that can either be diagnosed or treated using the claimed invention. Applicant had previously argued that the symptoms of Albright Hereditary Osteodystrophy (AHO) could be ameliorated by modulating the expression of LOBO. The Examiner rejected this argument arguing that reducing LOBO expression in such patient would either "do nothing or would exacerbate the condition". The Examiner's conclusion appears to be based on an erroneous assumption. That is to say that the loss of human LOBO function, alone, may be responsible for AHO. This is not the case. Although Example 7 postulates that LOBO may be the candidate gene for AHO, Example 7 also clearly states that a defect in one or more protein partners (e.g. the 20q13 G protein, LOBO, 2q37, etc.) may cause the visible phenotype observed in AHO patients. Example 7 further states that the type of mutation (i.e. a point mutation or a null mutation) can also influence the particular phenotype observed. Thus, it is not unreasonable to assume that certain AHO patients may benefit from the modulation of LOBO expression.

Finally, although Applicant's previous arguments focused on the potential use of the claimed compositions to treat AHO, it should be noted that Applicant also specifically stated the compositions could be used in the treatment of other diseases or disorders which involve growth disturbance (e.g., growth disturbance relating to bones) (See page 1—spondyloepiphyseal dysplasias such as achondrodysplasia). Achondrodysplasia, for example, is caused by dominant mutations in the fibroblast growth receptor 3 gene (FGFR3). Persons having a null mutation in the FGFR3 gene exhibit long bones whereas patients exhibiting a point mutation in the FGFR3 gene exhibit short bones. This difference shows that different mutations can result in completely different phenotypes, but also shows that, based on the disclosure in the Specification, a person

of ordinary skill in the art could reasonably conclude that persons suffering from this disease could by treated by modulating the expression of the LOBO protein.

The foregoing remarks demonstrate that the claims are supported by specific, substantial and credible utilities. Applicant further submits that a person skilled in the art would know how to use the claimed invention. As such, Applicant submits that the Specification meets the utility requirements of 35 U.S.C. § 101 and the enablement requirement under 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and removal of the rejection is respectfully requested.

5. Written Description

Claims 1-7, 20, 21, 23-26 and claims 8, 12, 13, 29 and 36-41 have been rejected under 35 U.S.C. §112, first paragraph, for failing to satisfy the written description requirement for the reasons set forth in the previous Office Action. The Examiner argues that the Specification fails to disclose or describe the specific structure of the proteins encoded by the claimed nucleic acid molecules that would distinguish them from other structurally similar proteins not embraced by the claims. Applicant respectfully traverses.

Claim 40 has also been rejected for reciting a limitation, "a homology of at least 97% to . . ." which is not supported by the Specification. Applicant would like to point out that the exact excerpt identified by the Examiner on page 9, first full paragraph, does indeed make reference to a degree of homology of at least 97%. Reconsideration and removal of the rejection with respect to claim 40 is therefore requested.

The claims as currently written are directed to nucleic acid sequences encoding a protein (either SEQ ID NO. 9 or SEQ ID NO. 14) or any nucleic acid sequences encoding a protein that has a homology of at least 70% to SEQ ID NO.9 or SEQ ID NO. 14. The Examiner maintains that Applicant has not established that a nexus between the structure of the proteins falling within this genus and the expected function of the protein (i.e. the reduction or inactivation of the protein results in bone elongation). Specifically, the Examiner states that the specific structures of the nucleic acids encoding the proteins have not been disclosed or described in such a way that would distinguish them from other structurally similar proteins not embraced by the claims.

The Examiner also states that the Application fails to identify the specific structural features of the proteins embraced from the claims which distinguish them from the structurally related but functionally different proteins described in the application. Finally, the Examiner states that Applicant has failed to establish that the human and LOBO proteins share the same function.

The claims as written only encompass a limited number of proteins that (1) share a specific percent homology with the human or murine LOBO protein and (2) when downregulated or inactivated in an animal result in the elongation of all bones with the exception of the skull bones. Applicant submits that the scope of the present claims is supported by the Specification and the Declaration of Dr. Rump submitted with Applicant's previous response. Pages 6-7 of the Specification describe the initial work performed by the inventors to characterize the LOBO gene and protein. The inventors compared the LOBO proteins to known proteins and demonstrated that the murine and human LOBO proteins belonged to a group of their own (see Fig. 6 and page 6, second full paragraph). The Specification goes on to state that the LOBO group is related to two other protein groups (VacB and RNAase II & Dis 3 proteins) and that the LOBO proteins may possess similar functions as these other group of proteins. The inventors do not state that the VacB, RNAaseII and Dis3 proteins are functional homologs of the LOBO protein. This is further supported by the BLAST search results summarized in the Declaration of Dr. Andreas Rump. The data demonstrated that ten proteins having a degree of identity of 70% of higher to the murine LOBO query sequence. The ten proteins were of human, murine or rat origin and Dr. Rump stated that given the high degree of sequence identity and similarity, he expected all of these proteins to share the same basic function as the murine LOBO protein. It should be noted the protein identified by accession number NP_014621, a Dis3 protein from *Saccharomyces cervisiae* only shared a 32% sequence identity with the query sequence and accordingly was not believed to share the same function. The foregoing remarks demonstrate that only proteins having the requisite degree of sequence homology to the murine or human LOBO proteins will possess the desired function.

Next, the Examiner focuses on the failure of the Application to demonstrate that the human and murine LOBO proteins possess the same function. Although the Examiner has acknowledged that Applicant cannot be expected to test whether knocking out the human LOBO

gene would produce a similar phenotype to knocking out the murine LOBO, he maintains that different phenotypes observed from the loss of gene function in Example 7 and the lack of any evidence linking the structure of the murine and human proteins to the function of human and murine proteins supports the rejection. Applicant respectfully disagrees.

The Examiner once again highlights the disclosure in Example 7 to support the rejection. While knocking out the LOBO gene in humans may result in a different phenotype than that observed in mice, this does not mean that the human and murine LOBO proteins do not share the same function. Example 7 clearly discloses that AHO results from the inactivation of more than one protein. Thus, the deletion of the LOBO gene in human AHO patients that manifests itself as hyposomia may be due to the fact that multiple proteins are responsible for the disease phenotype. Although Applicant cannot definitely establish the common function of the human and murine LOBO proteins through the use of knockout experiments, Applicant believes that the arguments presented in their last response with respect to the chromosomal location of the murine and human LOBO genes strongly supports their argument that the human and murine LOBO proteins share a common function.

Applicant had previously presented the following arguments to support their position that the disclosed mouse and human LOBO proteins are functional homologs:

(i) The application discloses that the identified mouse and human genes are localized on synthenic chromosomal regions (see Example 4 on page 27 and the paragraph bridging pages 10 and 11). This means that the murine gene is located on chromosome 1 in band 1D, a locus which corresponds to human chromosome 2, region 2q35-37, exactly the region where the human LOBO gene has been mapped.

(ii) The cDNA encoding the human LOBO protein and the cDNA encoding the mouse LOBO protein share a sequence identity of 85.2% (see Appendix II attached to the Declaration of Dr. Andreas Rump). The encoded proteins share a sequence identity of 88.1% (see Appendix I attached to the Declaration of Dr. Andreas Rump). Given that many amino acid changes are conserved (e.g. Lys-Arg, Glu-Asp, Leu-Ile, etc.), the similarity between the two proteins is actually even higher, namely 96.2% at the amino acid level. These high levels of sequence

identity on the nucleotide and the amino acid level between mouse and human over the entire sequence length is evidence that the human protein disclosed in the present application is indeed the functional homolog of the mouse LOBO protein. Moreover, Applicant submits that it is accepted in the art that in the art that in the case of polypeptides showing such a high degree of sequence identity (i.e., 88%) and sequence similarity (i.e., 96.2%), the polypeptides are expected to have the same function.

(iii) The inventors have produced antibodies against the recombinantly produced mouse LOBO protein disclosed in the present application. These antibodies also recognize the human LOBO protein of the present invention. These cross-reactivities are a very strong indication that the proteins are highly conserved and, thus, also exert the same function.

(iv) The inventors have shown the both the mouse and the human LOBO protein disclosed in the present application are specifically localized in the cytosol of the cell.

(v) Glycerol-gradient centrifugation experiments have shown that both the human and mouse LOBO proteins described in the present application are present in a high molecular weight complex.

The high sequence identity (over 80% at the nucleotide level, and even higher at the amino acid level) is strong evidence that the mouse and human sequence are indeed the same gene. This evidence coupled with the high degree of conservation between the human and murine LOBO proteins (88% sequence identity on the amino acid level and 85% sequence identity on the nucleotide level), in the opinion of Dr. Rump, a person of ordinary skill in the art, is strong evidence that the human and murine LOBO proteins would share the same function.

Applicant believes that the foregoing remarks demonstrate that the claims find adequate written description support in the Specification. Reconsideration and removal of the written description rejection is, therefore, respectfully requested.

6. Rejections under 35 U.S.C. §102(b)

Claim 7 has been rejected as anticipated by Browning et al. Applicant has amended claim 7 in accordance with the Examiner's suggestion in the Office Action of December 3, 2002. Reconsideration and removal of the rejection is respectfully requested.

7. Rejection under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 8 and 29 as being indefinite for omitting essential elements. Applicant has amended the claims to specify that the host cell is transformed by a nucleic acid molecule according to claim 1 comprising regulatory elements and then is cultured under conditions permitting expression of the protein. Applicant believes that the amendment has obviated the indefiniteness rejections and respectfully requests reconsideration and removal of the rejection.

Favorable action and early allowance of the claims are requested.

If the Examiner has any questions concerning this application, he is requested to contact Leonard Svensson (Reg. No.: 30,330) the undersigned at (714) 708-8555 in the Southern California area.

Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicant hereby petition for an extension of one (1) month to October 13, 2003 for the period in which to file a response to the Office Action dated June 13, 2003

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments: Copies of Sequence Listing submitted 8/27/01
Copies of Petition to Accept Color Drawings and/or Photographs (4/21/02)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: Oct. 14, 2003
(Date of Deposit)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

Susan Langworthy
(Signature)

Oct 14 2003
(Date of Signature)

## AMENDMENTS TO THE CLAIMS:

1. (Previously Presented) An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences encoding the amino acid sequence depicted in SEQ ID No. 9 or in SEQ ID No. 14;

(b) nucleic acid sequences depicted in SEQ ID No. 8 or SEQ ID No. 13;

(c) nucleic acid molecules encoding a protein, the amino acid sequence of which has a homology of at least 70% to the amino acid sequence of SEQ ID No. 9 or SEQ ID No. 14 ; and

(d) nucleic acid sequences deviating from the sequences mentioned in (c) on account of the degeneracy of the genetic code,

wherein the nucleic acid molecule encodes a protein, the reduction and/or inactivation of which in animals results in the elongation of the bones, with the exception of the skull bones.

2. (Previously Presented) The isolated nucleic acid molecule according to claim 1, which is genomic DNA.

3. (Original) The nucleic acid molecule according to claim 1, which is a cDNA molecule.

4. (Currently Amended) The isolated nucleic acid molecule according to claim 1, which is ~~an~~ RNA molecule.

5. (Original) A vector containing a nucleic acid molecule according to any one of claims 1 to 3.

6. (Original) The vector according to claim 5, wherein the nucleic acid molecule is linked to regulatory elements which ensure the expression of the nucleic acid molecule in prokaryotic or eukaryotic cells.

7. (Currently Amended) A host cell transformed by an isolated nucleic acid molecule according to ~~any one of~~ claims ~~1 to 4~~ 5 or claim 6.

8. (Currently Amended) A method for preparing a protein which is encoded by a nucleic acid molecule according to claim 1, which is linked to regulatory elements which ensure the expression of the nucleic acid molecule wherein a host cell is cultured under conditions permitting the expression of the protein and the protein is recovered from the cells and/or the culture medium.

9. (Withdrawn) A protein encoded by a nucleic acid molecule according to claim 1.

10. (Withdrawn) An antibody against the protein of claim 9.

11. (Withdrawn) A nucleic acid molecule which is a least 15 nucleotides long and specifically hybridizes to a nucleic acid molecule according to claim 1.

12. (Previously Presented) A diagnostic composition containing a nucleic acid molecule according to any one of claims 1 to 4.

13. (Previously Presented) A pharmaceutical composition containing a nucleic acid molecule according to any one of claims 1 to 4 and optionally a pharmaceutically acceptable carrier.

14. (Withdrawn) A method of preparing a transgenic non-human animal, wherein a nucleic acid molecule according to claim 1 is inserted into a germ cell, an embryonic cell, an egg cell, or a cell derived therefrom, and a transgenic animal is produced from the thus transformed cell.

15. (Withdrawn) A transgenic, non-human animal which is transformed with a nucleic acid molecule according to claim 1.

16. (Withdrawn) A transgenic non-human animal, wherein the expression of a protein according to claim 9 in the cells is lower than in cells of a corresponding wildtype animal.

17. (Withdrawn) The transgenic non-human animal according to claim 16, wherein at least one genomic copy of a gene which corresponds to a nucleic acid molecule according to claim 1, is inactivated.

18. (Withdrawn) The transgenic animal according to any one of claims 15 to 17, which is a non-human mammal.

19. (Withdrawn) The transgenic animal according to claim 18 which is a mouse.

20. (Previously Presented) A host cell transformed by a vector according to claim 5.

21. (Previously Presented) A host cell transformed by a vector according to claim 6.

22. (Withdrawn) A protein obtainable by the method of claim 8.

23. (Previously Presented) A diagnostic composition containing a vector according to claim 5.

24. (Previously Presented) A diagnostic composition containing a vector according to claim 6.

25. (Previously Presented) A pharmaceutical composition containing a vector according to claim 5.

26. (Previously Presented) A pharmaceutical composition containing a vector according to claim 6.

27. (Withdrawn) A method for preparing a transgenic non-human animal, wherein a vector according to claim 5 is inserted into a germ cell, an embryonic cell, an egg cell, or a cell derived therefrom, and a transgenic animal is produced from the thus transformed cell.

28. (Withdrawn) A method for preparing a transgenic non-human animal, wherein a vector according to claim 6 is inserted into a germ cell, an embryonic cell, an egg cell, or a cell derived therefrom, and a transgenic animal is produced from the thus transformed cell.

29. (Currently Amended) The method according to claim 8, wherein the host cell is transformed by an isolated nucleic acid molecule, linked to regulatory elements which ensure the expression of the nucleic acid molecule, selected from the group consisting of cDNA, genomic DNA and RNA.

30. (Withdrawn) A diagnostic composition comprising a protein according to claim 9.

31. (Withdrawn) A diagnostic composition comprising an antibody according to claim 10.

32. (Withdrawn) A diagnostic composition comprising a nucleic acid molecule according to claim 11.

33. (Withdrawn) A pharmaceutical composition comprising a protein according to claim 9 and optionally a pharmaceutically acceptable carrier.

34. (Withdrawn) A pharmaceutical composition comprising an antibody according to claim 10 and optionally a pharmaceutically acceptable carrier.

35. (Withdrawn) A pharmaceutical composition comprising a nucleic acid molecule according to claim 11 and optionally a pharmaceutically acceptable carrier.

36. (Previously Presented) An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences encoding the amino acid sequence depicted in SEQ ID No. 9;

(b) nucleic acid sequences depicted in SEQ ID No. 8;

(c) nucleic acid molecules encoding a protein, the amino acid sequence of which has a homology of at least 70% to the amino acid sequence of SEQ ID No.9; and

(d) nucleic acid sequences deviating from the sequences mentioned in (c) on account of the degeneracy of the genetic code,

wherein the nucleic acid molecule encodes a protein, the reduction and/or inactivation of which in animals results in the elongation of the bones, with the exception of the skull bones.

37. (Previously Presented) An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences encoding the amino acid sequence depicted in SEQ ID No. 9 or in SEQ ID No. 14;

(b) nucleic acid sequences depicted in SEQ ID No. 8 or SEQ ID No. 13;

(c) nucleic acid molecules encoding a protein, the amino acid sequence of which has a homology of at least 80% to the amino acid sequence of SEQ ID No. 9 or SEQ ID No. 14 ; and

(d) nucleic acid sequences deviating from the sequences mentioned in (c) on account of the degeneracy of the genetic code,

wherein the nucleic acid molecule encodes a protein, the reduction and/or inactivation of which in animals results in the elongation of the bones, with the exception of the skull bones.

38. (Previously Presented) An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences encoding the amino acid sequence depicted in SEQ ID No. 9 or in SEQ ID No. 14;

(b) nucleic acid sequences depicted in SEQ ID No. 8 or SEQ ID No. 13;

(c) nucleic acid molecules encoding a protein, the amino acid sequence of which has a homology of at least 90% to the amino acid sequence of SEQ ID No. 9 or SEQ ID No. 14 ; and

(d) nucleic acid sequences deviating from the sequences mentioned in (c) on account of the degeneracy of the genetic code,

wherein the nucleic acid molecule encodes a protein, the reduction and/or inactivation of which in animals results in the elongation of the bones, with the exception of the skull bones.

39. (Previously Presented) An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences encoding the amino acid sequence depicted in SEQ ID No. 9 or in SEQ ID No. 14;

(b) nucleic acid sequences depicted in SEQ ID No. 8 or SEQ ID No. 13;

(c) nucleic acid molecules encoding a protein, the amino acid sequence of which has a homology of at least 95% to the amino acid sequence of SEQ ID No. 9 or SEQ ID No. 14 ; and

(d) nucleic acid sequences deviating from the sequences mentioned in (c) on account of the degeneracy of the genetic code,

wherein the nucleic acid molecule encodes a protein, the reduction and/or inactivation of which in animals results in the elongation of the bones, with the exception of the skull bones.

40. (Previously Presented) An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences encoding the amino acid sequence depicted in SEQ ID No. 9 or in SEQ ID No. 14;

(b) nucleic acid sequences depicted in SEQ ID No. 8 or SEQ ID No. 13;

(c) nucleic acid molecules encoding a protein, the amino acid sequence of which has a homology of at least 97% to the amino acid sequence of SEQ ID No. 9 or SEQ ID No. 14 ; and

(d) nucleic acid sequences deviating from the sequences mentioned in (c) on account of the degeneracy of the genetic code,

wherein the nucleic acid molecule encodes a protein, the reduction and/or inactivation of which in animals results in the elongation of the bones, with the exception of the skull bones.

41. (Previously Presented) An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences encoding the amino acid sequence depicted in SEQ ID No. 9 or in SEQ ID No. 14;

(b) nucleic acid sequences depicted in SEQ ID No. 8 or SEQ ID No. 13;

(c) nucleic acid sequences, the complementary sequence of which hybridizes to the sequences mentioned in (a) or (b) under stringent conditions; and

(d) nucleic acid sequences deviating from the sequences mentioned in (c) on account of the degeneracy of the genetic code,

wherein the nucleic acid molecule encodes a protein, the reduction and/or inactivation of which in animals results in the elongation of the bones, with the exception of the skull bones.